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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/821,654	03/29/2001	Kenichi Hosoya	10939/2012	6149

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EXAMINER	
PAPPU, SITA S	

ART UNIT	PAPER NUMBER
1632	10

DATE MAILED: 01/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/821,654	HOSOYA ET AL.	
	Examiner	Art Unit	
	Sita S Pappu	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-14 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-14 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Preliminary amendment filed on September 17, 2001, in paper no.7, has not been entered. According to 37 C.F.R. 1.121, amendments to the specification/claims must be made by the submission of clean, new or replacement paragraph(s), section(s), or claim(s). The amendment submitted on September 17, 2001, does not provide a whole paragraph as required and, therefore, not entered. Please see attached copy of "Changes to the Patent Rules" explaining 37 C.F.R. 1.121.

Claims 1-14 are pending in the instant application and this paper contains an examination of the claims on their merits.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 (e) and 120 as follows:

Acknowledgment is made of applicant's claim for foreign priority based on a PCT application (filed on 10/01/1999) and two foreign applications (10-296138 and 10-296139 filed in Japan on 10/02/1998). It is noted, however, that applicant has not filed a certified copy of the foreign applications 10-296138 and 10-296139 as required by 35 U.S.C. 119(b). Need copy of the front with ribbon and seal included. No copy of the PCT application is provided.

Specification

The abstract of the disclosure is objected to because : abstract contains two paragraphs. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 4, 8 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the claims 4,8, and 12 refer to biological deposits to satisfy the "how to make" requirement, but fail to specify if they were made under the terms of the Budapest Treaty. If the deposits are made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific cell lines or cells have been deposited under the Budapest Treaty and that the cell line or cells will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and,

(d) a test of the viability of the biological material was performed at the time of deposit (see 37 CFR 1.807); and,

(e) the deposit will be replaced if it should ever become inviable.

Claim Rejections – 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-6 are rejected under 35 U.S.C. 102(a) as being anticipated by Hosoya et al. (2001; Exp. Eye Research, vol. 72, 163-172).

Hosoya et al. (2001) teach the immortalized cell which expresses a temperature sensitive SV40 large T-antigen gene, GLUT-1 transporter and p-glycoprotein derived from the retinal capillary endothelial cells of a transgenic rat into which a large T-antigen gene of SV40 temperature sensitive mutant tsA58 has been introduced. In particular, Hosoya et al. teach the TR-iBRB2 cells of the instant invention (see abstract, page 163).

Claims 7-10 are rejected under 35 U.S.C. 102(a) as being anticipated by Kitazawa et al. (2001; Pharmaceutical Research, vol. 18, no. 1, pp16-22).

Kitazawa et al. (2001) teach the immortalized cell which expresses a temperature sensitive SV40 large T-antigen gene, and shows localization of Na+-K+ ATPase and GLUT-1 transporter in the cell membrane and shows localization of the Na+-K+ ATPase in the apical side when cultured in a monolayer. Kitazawa et al. teach this cell as derived from choroids plexus epithelial cells of a transgenic rat into which a large T-antigen gene of SV40 temperature sensitive mutant tsA58 has been introduced. In particular, Kitazawa et al. teach the TR-CSFB1 through TR-CSFB5 of the instant invention (see abstract, page 16).

Claims 11-14 are rejected under 102(a) as being anticipated by Hosoya et al. (2000; Journal of Drug targeting, vol.8, no.6, pp357-370).

Hosoya et al. (2000) teach the immortalized cell lines that express GLUT-1 transporter, p-glycoprotein, alkaline phosphatase and γ-glutamyltransferase which cell lines were derived from brain capillary endothelial cells of a transgenic rat into which a large T-antigen gene of SV40 temperature sensitive mutant tsA58 has been introduced. In particular, Hosoya et al. (2000) teach the TR-BBB cell lines 1, 5, 6, 11, 13 of the instant invention.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Hosoya et al. (1999; IOVS, volume 40, no.4, pp. S466, Annual Meeting of the association for research in vision and ophthalmology, Fort Lauderdale, Florida, USA).

Hosoya et al. (1999) teach the immortalized cell which expresses a temperature sensitive SV40 large T-antigen gene, GLUT-1 transporter and p-glycoprotein derived from the retinal capillary endothelial cells of a transgenic rat into which a large T-antigen gene of SV40 temperature sensitive mutant tsA58 has been introduced. In particular, Hosoya et al. teach the TR-iBRB2 cells of the instant invention (see conference proceedings abstract, page S466).

Claims 1, 3, 6, 11 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Greenwood et al. (1996; Journal of Neuroimmunology, vol. 71, pp 51-63).

Claims 1, 3, 6, 11, and 14 are directed to immortalized and/or established cells derived from retinal capillary endothelial cells or brain capillary endothelial cells obtained by the claimed methods.

Claims 1, 3, 6, 11 and 14 are product-by-process claims. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. The patentability of a product does not depend on its method of production. See M.P.E.P. 2113. Thus, the claims read on immortalized cells disclosed in the prior art as discussed below.

Greenwood et al. disclose immortalized retinal and brain endothelial cells (see abstract). These cell lines express the GLUT-1 glucose transporter and the p-

glycoprotein (column 2, paragraph 4) and contain an SV40 T-oncogene (column 2, paragraph 8). These cell lines were produced by the dispersion of the tissue by enzymatic digestion (see page 53, left column, paragraph 2, lines 4-6). In addition, these cell lines express all of the markers ubiquitous to endothelia as well as specific markers characteristic of CNS endothelia (page 60, paragraph 1, left column, lines 20-23). These markers include alkaline phosphatase and gamma-glutamyl transferase that are specific to endothelial cells. The expression of these markers is an inherent property of the CNS endothelial cells. Therefore, even though Greenwood et al. (1996) did not specifically disclose expression of the alkaline phosphatase and gamma-glutamyl transferase in the prior art, the expression of said markers is considered inherent to the cell lines disclosed by Greenwood et al. (1996).

In the absence of evidence to the contrary, the immortalized cells disclosed and claimed (claims 1, 3, 6, 11 and 14) by Greenwood et al. meet the structural limitations of the instantly claimed cells and are the same as those instantly claimed.

Thus, Greenwood et al. (1996) disclose the immortalized cells as instantly claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 6, 7, 10, 11, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rudland et al. (1997; PCT International application publication no. WO 97/39117) and Greenwood et al. (1998; U.S. Patent Number 6090624), further in view of Roux et al. (1994; Journal of cellular physiology, vol.159, pp.101-113) and Villalobous et al (1997; Journal of pharmacology and Experimental therapeutics, vol.282, pp. 1109-1116).

Claims 1-3, 6, 7, 10, 11, and 14 are product-by-process claims. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. The patentability of a product does not depend on its method of production. See M.P.E.P. 2113. Thus, the claims read on immortalized cells disclosed in the prior art as discussed below.

Claims 1-3, 6, 11, and 14:

Rudland et al. (1997) teach conditionally immortalized cell lines from brain of transgenic rats expressing the SV40 temperature-sensitive mutant large T antigen mutant tsA58 gene, isolated using collagenase (page 32, lines 3-6) and trypsin (page 39, lines 20-22) digestion.

Rudland et al. (1997) do not teach the immortalized cells from the retinal capillary and brain capillary endothelial cells.

Greenwood et al. (1998) teach the immortalized cells from retinal capillary endothelial cells that express the GLUT-1 transporter and p-glycoprotein.

Greenwood et al. (1998) do not explicitly teach the immortalized cells from brain capillary endothelial cells. However, Greenwood et al. (1998) teach that the retinal capillary and brain capillary endothelial cells are considered to have an identical structure (column 1, lines 19-24). Further, the markers, alkaline phosphatase and gamma-glutamyl transferase are specific to endothelial cells in addition to the GLUT-1 transporter and the p-glycoprotein . The expression of these markers is an inherent property of the CNS endothelial cells, which include the brain capillary endothelial cells, as stated by Roux et al. (1994; page 101, left column, paragraph 1).

The motivation to combine the teachings of Rudland et al. and Greenwood et al. was provided by both Rudland et al and Greenwood et al. Rudland et al. suggested that their invention is useful in toxicological and pharmacological studies, and that their invention should be amenable to use in other tissues to generate conditionally immortal cell lines (page 11, paragraph 1) . Greenwood et al. (1998) state that their retinal cell lines are capable of conveying a substance of therapeutic interest into the eye and the central nervous system and serve as model for studying the blood central nervous system interfaces (column 1, paragraph 2) and that both the blood-brain barrier and the blood retina-barrier are important in controlling the passage of substances to and from the neural parenchyma (column 1, paragraph 3).

Therefore, it would have been obvious to one of ordinary skill in the art to use the transgenic rat of Rudland et al. to prepare immortalized retinal capillary endothelial cell lines, with a reasonable expectation of success. Further, it would have been obvious to develop immortalized brain capillary endothelial cell lines, considering the identical structure with retinal capillary endothelial cells, and the shared functional similarity in controlling the passage of substances to and from the neural parenchyma.

Claims 7 and 10:

Rudland et al. (1997) teach conditionally immortalized cell lines from brain of transgenic rats expressing the SV40 temperature-sensitive mutant large T antigen mutant tsA58 gene, using collagenase (page 32, lines 3-6) and trypsin (page 39, lines 20-22) digestion.

Rudland et al. (1997) do not teach the immortalized choroid plexus cells with their transgenic rat.

Greenwood et al. (1998) also do not teach the immortalized choroid plexus cells.

However, Greenwood et al. (1998) teach immortalized retinal pigmentary epithelial cells (see abstract) and state that they are similar to the choroid plexus epithelial cells (column 1, lines 24-29).

The motivation to combine the teachings of Rudland et al. and Greenwood et al. was provided by both Rudland et al and Greenwood et al. Rudland et al. suggested that their invention is useful in toxicological and pharmacological studies, and that their invention should be amenable to use in other tissues to generate conditionally immortal

cell lines (page 11, paragraph 1). Greenwood et al. (1998) state that their retinal cell lines are capable of conveying a substance of therapeutic interest into the eye and the central nervous system and serve as model for studying the blood central nervous system interfaces (column 1, paragraph 2 and also see abstract).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Rudland et al. and Greenwood et al. to prepare immortalized choroid plexus epithelial cell lines, with a reasonable expectation of success, considering the similarity with retinal pigmentary epithelial cells.

Similar to the endothelial cells of the CNS, the expression of the markers, Na^+-K^+ ATPase and GLUT-1 transporter in the cell membrane, and the localization of the Na^+-K^+ ATPase in the apical side when cultured in a monolayer is an inherent property of the choroids plexus cells (Villalobous et al. 1997; page 1111, right column, paragraph 2).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (9:00 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached on (703) 305-6608. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications. Any inquiry of a general nature or relating to the status of

this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-2758.

S. Pappu
December 17, 2001

Anne-Marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER